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Management of Patients with Hyperlactataemia / Lactic Acidosis

Hyperlactataemia is a mitochondrial toxicity associated with nucleoside reverse transcriptase inhibitor (NRTI) therapy. All NRTIs have been associated with hyperlactataemia, especially the combination of stavudine and didanosine. Abacavir and lamivudine are least associated, whilst the nucleotide RTI tenofovir (TDF) has not been implicated. Symptomatic hyperlactataemia occurs in about 1-2% per annum of patients on NRTI therapy whereas lactic acidosis (hyperlactataemia resulting in metabolic acidosis) occurs in 0.1-0.4%. Hyperlactataemia usually occurs after patients have been on NRTIs for several months (median 9 months) and results from mitochondrial damage induced by these drugs. Typically the patients are responding well to HAART. The mortality rate with lactic acidosis is 30-60%.

The onset is often with non-specific features, but the most important warning signs are unexplained weight loss (especially >5%) and abdominal symptoms (pain, nausea and vomiting). Other features of mitochondrial toxicity, notably peripheral neuropathy, are often present. Tachypnoea secondary to acidosis is a late sign.

Clinical assessment should include evaluation of respiratory rate and abdominal examination. Investigations should include lactate level, standard bicarbonate, LFTs and lipase. The latter two are to exclude concomitant steatohepatitis or pancreatitis. Management depends on symptoms, lactate level, standard bicarbonate and ability to monitor lactate on rechallenge. Metabolic acidosis is defined here as standard bicarbonate < 20 (the pH may be normal due to respiratory compensation). Suggested management:

- In patients with mild hyperlactataemia (Lactate 2.5-5 and no metabolic acidosis) the NRTI combination should, if possible, be switched to lamivudine plus either abacavir or tenofovir. Another approach is to switch stavudine to zidovudine. The lactate should be rechecked within 3 days and then weekly until normalised. If the lactate continues to rise despite this switch then all drugs should be stopped and a rechallenge as described below commenced once the lactate has normalised.

- Patients with moderately severe hyperlactataemia (lactate 5-10 without significant metabolic acidosis – i.e. standard bicarbonate > 15) should stop HAART and preferably be observed as an inpatient for 1-2 days, given oral B vitamins (BCo 2 tabs bd and thiamine 100mg bd) , well hydrated (orally or IVI) and have sepsis and opportunistic infection excluded.

  HAART should only be recommenced when lactate has normalized (this will usually take weeks) and the decision regarding what regimen to restart should be discussed with the AfA clinical committee.

  The decision as to what to recommence is either:
  (1) Lamivudine, NNRTI with one of abacavir or tenofovir. If this is done lactate monitoring should be done at 2 weeks, 4 weeks and then monthly for a further 2 months and at any time symptoms recur.
  (2) NNRTI with Kaletra® (Kaletra® dose here is 4 capsules bd due to NNRTI induction of Kaletra® metabolism). If patient has NNRTI resistance then a dual-boosted PI regimen (Kaletra® plus Invi-rase®) is an option.

  There is no risk of recurrence of hyperlactataemia with (2) whereas with (1) there is a small risk that hyperlactataemia may recur.

- Patients with severe hyperlactataemia (lactate > 10 without metabolic acidosis) or significant lactic acidosis (raised lactate regardless of level with standard bicarbonate < 15) should preferably be managed in a high care facility:
  - Stop HAART
  - IVI thiamine 100mg 12hrly and BCo 1 amp 12hrly
  - IVI fluids
  - Blood culture/ urine culture/ septic search AND empiric broad spectrum antibiotics (e.g. a third generation cephalosporin) - this is important because septicaemia may cause lactic acidosis and mimic drug induced lactic acidosis
  - Consider IVI $NaHCO_3$ if profound acidosis
  - Consider ventilation if respiratory fatigue occurs

These patients should be recommenced on Kaletra® 4 capsules bd and NNRTI (or dual-boosted PI regimen) when lactate has normalized (this may take weeks). These patients should not be rechallenged with an NRTI.

Other manifestations of NRTI mitochondrial toxicity that may occur in association with hyperlactataemia are steatohepatitis, peripheral neuropathy, pancreatitis, myopathy, cardiomyopathy and a neuromuscular weakness syndrome resembling Guillain Barre syndrome.

It is important to remember that there are other causes of hyperlactataemia and the drugs are not always the culprit. These include sepsis, severe anaemia, hepatic failure, pancreatitis, severe cardiac failure, severe dehydration and thiamine deficiency.

Practice point
OF THE MONTH

Storage of Kaletra®

Kaletra® capsules and solution should be stored in a refrigerator (2 - 8ºC) until dispensed. Refrigeration is not required by the patient if used within 42 days and stored below 25ºC.

Doses in Renal Failure

For peritoneal dialysis the dose given under creatinine clearance <10 should be given daily. For haemodialysis the dose given under creatinine clearance <10 should be given daily, but must be given after dialysis on dialysis days as the drug will be dialysed out.

Formula to estimate creatinine clearance:

$$\frac{(140 - \text{age}) \times \text{ideal weight(kg)}}{0.82 \times \text{serum creatinine (µmol/L)}}$$

Good estimate for men, for women multiply total by 0.85

Drug	Creat. clearance 10-50	Creat. clearance <10
Zidovudine	unchanged	300 mg daily
Didanosine	>60kg 200mg daily <60kg 150mg daily	>60kg 100mg/day <60kg 75mg/day
Lamivudine	150 mg daily	50 mg daily
Stavudine	>60kg 20mg 12 hrly <60kg 15mg 12 hrly	>60kg 20mg/day <60kg 15mg/day
Abacavir	unchanged	unchanged
Tenofovir	AVOID	AVOID
PIs	unchanged	unchanged
Nevirapine	unchanged	unchanged
Efavirenz	unchanged	unchanged
Co-trimoxazole	480mg daily	480mg three times a week
Fluconazole	half dose	quarter dose

Sources: Bartlett JG. Medical care of patients with HIV Infection 2003. The Sanford guide to antimicrobial therapy 2003.

Enteric Coated Videx® Capsules Available

Videx® EC has been launched and is available from wholesalers. Videx® EC is available as a 250mg capsule (cost price = R156.81 incl. VAT for 30) and a 400mg capsule (cost price = R202.38 incl. VAT for 30).

The dose of Videx® EC is 400mg / day for patients with a weight > 60kg and 250mg / day for patients with a weight < 60kg. Videx® EC should be taken on an empty stomach at least 1 hour before or 2 hours after a meal.

The benefits of Videx® EC over the buffered tablet form include better tolerability (nausea, bloating and diarrhoea significantly reduced), minimal drug interactions with the Videx® EC and a reduced pill burden.

AfA will not apply MPL to Videx® EC capsules. Please contact AfA on 0800 227 700 or +27 21 514 1768 or afa@afadm.co.za to switch your patients from didanosine tablets to Videx® EC capsules.

HAART Hypertension

A recent large cohort study has investigated the impact of antiretroviral therapy and HIV on the risk of hypertension. HIV-infected subjects not on antiretroviral therapy had lower risks of systolic hypertension. However those subjects on long-term (defined as >2 years) HAART were 51% more likely to have systolic hypertension.

The effect was modest, but coupled with the other adverse metabolic consequences of HAART (dyslipidaemia, insulin resistance and increased waist:hip measurements) is likely to increase the risk of developing atherosclerosis. It is important to periodically measure blood pressure in patients on HAART and treat confirmed cases of systolic hypertension.

Lifestyle changes should be tried first. Most conventional anti-hypertensive agents can be safely used with HAART, with the exception of the calcium channel blockers which are affected by drug interactions interfering with their metabolism by the cytochrome P450 system (calcium channel blocker levels are lower when co-administered with NNRTIs and higher with PIs).

Reference

Seaberg EC, Munoz A, Lu M, et al. Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003. AIDS 2005;19:953–960.

Drug interaction
OF THE MONTH

Clarithromycin and the Antiretrovirals

There is a drug interaction between clarithromycin and the protease inhibitors and clarithromycin and the non-nucleoside reverse transcriptase inhibitors (NNRTIs).

When clarithromycin is given with a protease inhibitor the clarithromycin levels will be increased. A dose reduction of the clarithromycin is only considered necessary if the patient has renal impairment.

When clarithromycin is given with the NNRTIs the clarithromycin levels are decreased, **BUT** the levels of the active metabolite of clarithromycin is increased. The active metabolite of clarithromycin has no activity against MAC. If the clarithromycin is being used to treat MAC, azithromycin 500mg/day should be used as an alternative. If the clarithromycin is being used to treat any other condition no dose change is needed.

Printed versions of the 5th Edition of the AfA Clinical Guidelines are available. Please send us an e-mail (afa@afadm.co.za) with your postal address or phone 0860 100 646 if you would like us to send you a free copy.